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Are progestins really necessary as part of a combined HRT regimen?

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ABSTRACT

For many years it has been perceived wisdom that HRT for women with a uterus should include a progestin to prevent the proliferative effects of estrogen on the endometrium and endometrial cancer. But, with the reports from the Women's Health Initiative and Million Women Study indicating that such regimens are associated with an increased risk of breast cancer, whereas unopposed estrogen may not increase this risk, or even reduce it, it is pertinent to reassess the merits of adding a progestin. In addition, the suggestion from the WHI that the effects of estrogen and progestins are a 'class effect' are clearly inaccurate, as there is particular evidence from the French E3N cohort studies of differential effects of progestins with progesterone and dydrogesterone additions showing no increase in risk of breast cancer. The data are presented but an answer to the posed question remains unclear and as usual dependent on the circumstances and views of each individual woman and her medical adviser.

Introduction

It has been widely advocated that Progestins be added to hormone replacement therapy (HRT) regimens since the 1970's when the evidence that unopposed estrogen caused endometrial hyperplasia and cancer was highlighted by several reports from the west coast of USA[1-3]. Initially this was by sequential addition of 7-14 days in each month, with the production of a withdrawal bleed and endometrial shedding and more recently the continuous combined regimens have been promoted, which keep the endometrium atrophic and reduce the incidence of unacceptable bleeding. However, it is the progestin element of HRT which causes most of the mild side-effects, such as premenstrual-type symptoms, but more importantly seems to be the main factor that increases the risk of breast cancer, as shown in the Women's Health Initiative (WHI) reports [4-6]. The Million Women observational study(MWS)[7] from the United Kingdom also implicated the role of additional progestin and prompted the comment that there is "…little advantage to using oestrogen-progestogen in preference to oestrogen-only HRT for women who still have a uterus". This paper will review the data on the role of progestin in HRT, the merits of different regimens and types of progestin to help in answering the question.

Endometrial hyperplasia and cancer

1.Sequential HRT

Endometrial cancer remains an important cause of morbidity and mortality among women worldwide, although the incidence is much higher in the developed world. One risk factor is a delayed or late

menopause, so HRT which effectively prolongs the menopausal age could increase the risk. The ideal HRT regimen will relieve menopausal symptoms without increasing the risk of hormone dependant disease, but the possibility of causing endometrial or breast cancers dominate current prescribing practice. Unopposed estrogen is associated with a significant increased risk of irregular bleeding, endometrial hyperplasia and cancer. A Cochrane review of all the appropriate studies[8] found that after 6 months of unopposed estrogen, the odds ratio(OR) of developing endometrial hyperplasia was 5.4 (95% confidence interval (CI) 1.4-20.9) and after 36 months was 16.0 (95%CI 9.3-27.5). Prolonged use of unopposed estrogen is associated with progression to endometrial cancer with relative risks (RR) upwards of 1.4[1,2] and increasing with duration to 15.0[3]. Furthermore it is not widely recognised that the risk of endometrial cancer remains increased for many years after stopping unopposed estrogen[9]. Even after 15 years or more without therapy there is still a significantly increased RR of 5.8 (95% CI 2.0-17). To counteract this risk, progestins have been added to estrogen replacement therapy in a sequential regimen for usually 10-14 days in each cycle, with the intention of imitating the normal pre-menopausal ovarian cycle, and producing a regular and predictable withdrawal bleed, which can be beneficial for many women experiencing irregular peri-menopausal bleeding and menopausal symptoms.

Estrogen causes endometrial proliferation by increasing the number of estrogen/progesterone receptors and also increasing the mitotic rate in the glandular cells of the endometrium. The administration of progestin during estrogen therapy causes a down-regulation of the receptors and induction of 17β-estradiol dehydrogenase, which converts estradiol to the less active estrone, thereby reducing the estrogenic stimulus[10]. The histological evidence of a progestin effect

is a change from a proliferative to a secretory endometrium from which hyperplasia is less likely to develop. The effects of sequential regimens have been much studied and have confirmed that the progestin addition does reduce the incidence of endometrial hyperplasia and that this is greater with 12-13 days of progestin per cycle compared to fewer days[11]. However, with longer duration of HRT use the protective effect seems to diminish. One study of 1106 women taking sequential therapy containing 10-12 days of progestin, for a mean of 3.29 years found a secretory endometrium in 47.5%, but complex hyperplasia in 5.3% and atypical hyperplasia in 0.7%[12]. This compares with the findings in peri- and post-menopausal women without symptoms of a 5.2% incidence of endometrial hyperplasia[13]. After three years of sequential HRT the PEPI trial[14] reported a 1.7% prevalence of hyperplasia compared to 0.8% on placebo and Weiderpass[15] found that the RR of endometrial cancer with sequential therapy increased from 1.5 (95%CI 1.0-2.2) with less than five years use to 2.9 (95%CI 1.06-1.15) with more than five years use.

As monthly sequential therapy results in a cyclical bleed, which is inconvenient for some women and may reduce compliance, attempts have been made to limit the frequency of bleeding by longer sequential cycles ranging from 3 to 6 months. However, David and colleagues[16] demonstrated that simple hyperplasia develops after just three months of unopposed estrogen, so this has been generally considered to be the maximum interval for adding progestin. The Scandinavian Long Cycle Study Group[17] compared monthly with three monthly sequential therapy and found that the incidence of endometrial pathology (simple, complex or atypical hyperplasia, or cancer) was significantly higher in the three monthly cycle group (P = 0.0003), with an annual incidence of 5.6% as

compared to 1% in the monthly cycle group. They further confirmed that long-cycle therapy resulted in more irregular bleeding but no improved compliance. Conversely, another study from Finland found no increase in hyperplasia over 5 years using a combination of estradiol valerate 2mg and MPA 20mg[18].

All these data indicate that progestins will reduce the risk of endometrial; hyperplasia and cancer, but that the duration of progestin in each cycle is important and should be for at least 10 days. Furthermore there may still be a risk with long term use of monthly sequential HRT and probably more so with long-cycle regimens.

2. Continuous combined therapy

The biochemical and morphological changes in the endometrium induced by progestin are maintained as long as the progestin is administered[19]. If this is continuous, the proliferative effect of estrogen will be prevented and the endometrium should become atrophic. This was the rationale for the introduction of continuous combined therapy (CCT)[20], since without any cycle or a progestin phase, and with no tissue to be shed, there should not be any bleeding, whereas the benefits should be the same as for sequential therapy. Although the main aim of CCT is to avoid cyclical bleeding, all studies of CCT have found a high incidence of bleeds, particularly in the first three months, varying from 50-80%. This occurs more often in women who are within one year of the menopause rather than postmenopausal[21,22]. However, once the bleeding has subsided, amenorrhoea is usually maintained indefinitely.

Many studies have confirmed that an atrophic endometrium is achieved with CCT in 90-100% of women, even after only 3 months of treatment with daily doses of progestin as low as 0.25mg/day norethisterone acetate or 2.5mg/day of medroxyprogesterone acetate (MPA). After one year of treatment with conjugated equine estrogens (CEE) 0.625mg/day and MPA 2.5 or 5.0mg/day, Woodruff and Pickar[23] found endometrial hyperplasia without atypia in <1% of women, which is less than the background rate in postmenopausal women. The Cochrane review reported that endometrial hyperplasia may be less likely with CCT than a sequential regimen, in particular with long duration of therapy; OR 0.3 (95%CI 0.1-0.97)[8].

In the UK a multicenter study reported on 751 women who had previously been taking sequential HRT and 445 untreated postmenopausal women (total 1196) who completed 9 months of CCT with estradiol 2mg/day and norethisterone acetate 1mg/day[12]. There were no cases of endometrial hyperplasia and the endometrium was atrophic in more than two thirds of the women. Furthermore, all the women with complex hyperplasia during their prior sequential HRT and who completed the study (n=42) reverted to normal endometrial patterns. Continuation of this study for 5 years confirmed the protective effect of this CCT regimen in 387 women, with >70% having an atrophic endometrium and the remainder having other normal histology and no hyperplasia or cancer[24]. These data indicate the protective effect of the continuous progestin of CCT regimens not only in preventing hyperplasia but also the correction of pre-existing hyperplasia.

Assuming that endometrial carcinoma will usually develop from hyperplasia, the prevention of hyperplasia with CCT should also prevent cancer. A population-based control study in Sweden reported that with less than five years of CCT the observed risk of

developing cancer was 0.8 (95%CI 0.5-1.3) and with more than five years use it was 0.2 (95%CI 0.1-0.8)[15]. The largest randomised controlled trial of HRT, the WHI study, reported that after CCT with CEE 0.625mg/day and MPA 2.5mg/day for a mean of 5.3 years in 8506 women, there was no change in the risk of endometrial cancer compared to the placebo arm. The hazard ratio(HR) was 0.63 (95%CI 0.47-1.47)[25]. However, the MWS reported that with last use of a CCT regimen the risk of endometrial cancer was significantly reduced, the relative risk being 0.71 (95%CI 0.56-0.90) $p = 0.005$[26] (table 1). Since these studies were designed and partly as a result of their reporting and National Regulatory Authorities responses, there has been a move to the use of lower doses of estrogen and progestins than used in the WHI studies and ultra-low dose CCT regimens are now available. Estradiol 0.5 mg is the lowest dose that is effective in relieving vasomotor symptoms[27] and combined with either 2.5mg dydrogesterone or 0.1mg norethisterone also has less stimulation of the endometrium and very acceptable amenorrhoea rates compared with higher dose regimens[28-31].

Progestins are added to HRT solely to protect the endometrium from the proliferative effects of estrogen, so it is logical to deliver the progestin directly to the endometrial cavity. An intrauterine system delivering levonorgestrel has been available for many years for the management of menorrhagia and contraception (Mirena®), but has also been used as part of CCT regimens and provides excellent endometrial protection[32,33].

Adherence with HRT

Some side effects are experienced by most women taking HRT but in many they are mild and transient and with appropriate counselling should not affect continuation. However, reports of the rates of

discontinuation of HRT vary widely and are dependent on many factors such as the indication for taking HRT, the quality of the initial consultation and patient information/discussion, patient expectation, type of HRT, side effects, anxiety about safety, especially breast cancer. The most frequent reasons given for discontinuation are bleeding and weight gain and pre-menstrual-type symptoms such as bloating, headaches and breast tenderness[34,35]. Many of these are less common in those who have had a hysterectomy and are taking unopposed estrogen, so they are attributable to the progestin component. Strategies to counter these problems require individualisation of treatment and include changing to a different type of progestin or using natural progesterone, reducing the dose or route of administration. For the rare cases of severe progestin intolerance and who need estrogen for menopausal symptoms, unopposed estrogen may be given and the endometrium monitored by regular transvaginal ultrasound. When the endometrium becomes more than 5mm thick a course of progestin is given to arrest proliferation and cause endometrial shedding[36]. This management strategy requires good patient compliance and reliable ultrasound scanning.

Hormones and the breast

The differential effects of estrogens and progestins/progesterone on the breast have been the subject of considerable study and debate for many years, and especially since the WHI study reports. While progestins protect the endometrium from the proliferative effects of estrogen in postmenopausal women taking HRT, this is not replicated in the breast[37]. Indeed, during the menstrual cycle it is evident that peak proliferation of breast tissue occurs during the late luteal phase when natural progesterone levels are maximal, but also there is an increase in apoptosis at this time[38]. The WHI study has confirmed this

differential effect with a lower incidence of invasive breast cancer after the use of unopposed CEE for a median of 5.9 years, HR 0.77 (95%CI 0.62-0.95)[39], whereas the combined CEE and MPA arm was associated with a non-significant trend towards an increased risk HR 1.26 (adjusted 95%CI 0.83-1.92)[4]. But the media reporting of the initial paper of an increase in breast cancer of 26% implied a significant risk, and with banner headlines in newspapers across the world, a generation of women and doctors have remained mostly now too frightened to consider taking or prescribing HRT. In addition the comments from the authors that this was demonstrating a class effect of HRT implied that no HRT was safe. The subsequent report from the MWS of an even greater risk with all types of HRT and especially with combined estrogen and progestin regimens compounded the fears[7]. In contrast to endometrial cancer, the risk of breast cancer declines back to baseline within five years after cessation of HRT[40].

In countries outside North America, MPA is used much less than a wide range of other progestins with varying metabolic effects, though similar endometrial protection. The E3N is a prospective cohort initiated in France in 1990 to investigate the risk factors for cancer in women. In particular it has addressed breast cancer and associations with different types and regimens of HRT. During follow-up (mean duration 8.1 postmenopausal years), 2354 cases of breast cancer occurred among 80,377 postmenopausal women. Compared with women who had never used HRT, women who used estrogen alone had 1.29-fold increased risk (95%CI 1.02-1.65). The association of combined estrogen and progestin regimens with breast cancer risk varied significantly according to the type of progestin. The RR was 1.00 (95%CI 0.83-1.22) for estrogen-progesterone, 1.16 (95%CI 0.94-1.43) for estrogen-dydrogesterone, and 1.69 (95%CI 1.50-1.91) for

estrogen combined with other progestins (Table 2). The other progestins included – medrogestone, chlormadinone acetate, cyproterone acetate, promegestone, nomegestrol acetate, norethisterone acetate and MPA, but their associations with breast cancer risk did not differ significantly from each other[41]. These findings suggest that the choice of progestin in combined HRT regimens may be important regarding breast cancer risk and confirms that there is no class effect of HRT. It is therefore time that the WHI investigators stop referring to their data with CEE and MPA as estrogen and progestin and recognise the difference, as in the latest paper from the observational arm, reporting after a mean of 11.3 years of combined therapy a HR of 1.55 (95%CI 1.41-1.70; $P<0.001$)[42].

The dose as well as type of progestin may also be important in contributing to the risk of breast cancer. New ultra-low dose combined regimens have no effect on endometrial thickness and one combination of estradiol 0.5mg with norethisterone 0.1mg did not cause any detectable change in breast density over 6 months[43]. It is unlikely ever to be tested in a large enough randomized study to identify the outcome for breast cancer.

The intrauterine delivery of the progestin levonorgestrel results in lower circulating levels than with oral administration but a case-control study has shown an increased risk of breast cancer when used alone or in combination with estradiol[44,45].

Conclusions

The type and regimen of HRT should always be tailored to the individual woman, so the answer to the title question will depend on assessment of the risks and benefits of each strategy, weighing up the evidence and coming to a joint informed decision of the woman

with her medical adviser. Hysterectomy rates globally may be decreasing with the wider use of endometrial ablative techniques, intrauterine progestin-releasing systems and effective medical managements, so the proportion of women reaching the menopause and potentially at risk of endometrial cancer may increase. It is for these women that the decision on the use of progestins with HRT is pertinent. The evidence presented above may be condensed in to the following points for either unopposed estrogen or the combination with a progestin:

In favour of unopposed estrogen	***In favour of additional progestin***
Additional progestin associated with greater risk of breast cancer	Unopposed estrogen associated with significantly increased risk of endometrial hyperplasia and cancer
Very small risk of breast cancer with unopposed estrogen	Additional progestin can protect from endometrial hyperplasia and cancer
Fewer symptomatic side-effects; no cyclical PMS-type symptoms	Unopposed estrogen may cause irregular bleeding which can be controlled/prevented by progestins
Risk of endometrial cancer much less over short duration of use	Progesterone and dydrogesterone may not increase risk of breast cancer
Easier administration	Risk of endometrial cancer remains for many years after cessation of unopposed estrogen

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Legends for tables:

Table 1.

Summary of relative risks (RR) and 95% confidence intervals (CI) for endometrial cancer with different durations of unopposed estrogen, sequential and continuous combined estrogen and progestin (CCT); data from Grady et al[46]; Wiederpass[15]; Anderson et al[25]; Beral et al[26].

Table 2

Risks for invasive breast cancer by type and duration of exposure, compared with HRT never-use. (From ref 41 with permission)

[[a]PY= person-years; [b] adjusted for covariates; [c] orally or vaginally administered promestriene or estriol; [d] Intramuscularly administered estrogen or progestogen, androgen, nasally administered progestogen, or tibolone; [e]women who did not use the same class of HRT throughout follow-up contribute person-years to this "mixed" category from the time they changed class.]

Table 1

Type of HRT	RR	95% CI
Unopposed estrogen <1yr	1.4	1.0-1.8
1-4 yrs	2.8	2.3-3.5
5-9 yrs	5.9	4.7-7.5
10+ yrs	9.5	7.4-12.3
Sequential E + P < 5yrs	1.5	1.0-2.2
>5yrs	2.9	1.8-4.6
CCT (MWS)	0.7	0.6-0.9
CCT (WHI) 5.3yrs	0.6	0.5-1.5
CCT >5yrs	0.2	0.1-0.8

Table 2.

HRT type and duration of exposure (years)	Cases/PY [a]	Relative risk [b] (95%CI)
None	**766/244,632**	**1 (ref)**
Estrogen alone	**76/20,347**	**1.29 (1.02-1.65)**
<2	24/6,747	1.26 (0.83-1.89)
[2-4[	18/5,705	1.13 (0.70-1.81)
[4-6[	14/3,172	1.50 (0.88-2.56)
6+	13/3,301	1.31 (0.76-2.28)
p for trend		0.73
Estrogen + progesterone	**129/40,537**	**1.00 (0.83-1.22)**
<2	18/8,697	0.71 (0.44-1.14)
[2-4[	33/11,647	0.95 (0.67-1.36)
[4-6[	30/7,619	1.26 (0.87-1.82)
6+	43/10,111	1.22 (0.89-1.67)
p for trend		0.04
Estrogen + dydrogesterone	**108/31,045**	**1.16 (0.94-1.43)**
<2	16/6,923	0.84 (0.51-1.38)
[2-4[	28/8,697	1.16 (0.79-1.71)
[4-6[	21/5,590	1.28 (0.83-1.99)
6+	35/7,876	1.32 (0.93-1.86)
p for trend		0.16
Estrogen + other progestagens	**527/104,243**	**1.69 (1.50-1.91)**
<2	86/22,792	1.36 (1.07-1.72)
[2-4[	134/30,189	1.59 (1.30-1.94)
[4-6[	106/19,942	1.79 (1.44-2.23)
6+	156/23,817	1.95 (1.62-2.35)
p for trend		0.01
Weak estrogens [c]	**56/17,091**	**0.90 (0.68-1.18)**
Others [d] / unknown HRT	**82/21,071**	**1.27 (1.01-1.60)**
Mixed [e]	**538/130,594**	**1.25 (1.11-1.41)**